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# Association of Mild to Moderate Chronic Kidney Disease With Venous Thromboembolism

## Pooled Analysis of Five Prospective General Population Cohorts

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**Background**—Recent findings suggest that chronic kidney disease (CKD) may be associated with an increased risk of venous thromboembolism (VTE). Given the high prevalence of mild-to-moderate CKD in the general population, in depth analysis of this association is warranted.

**Methods and Results**—We pooled individual participant data from 5 community-based cohorts from Europe (second Nord-Trøndelag Health Study [HUNT2], Prevention of Renal and Vascular End-stage Disease [PREVEND], and the Tromsø study) and the United States (Atherosclerosis Risks in Communities [ARIC] and Cardiovascular Health Study [CHS]) to assess the association of estimated glomerular filtration rate (eGFR), albuminuria, and CKD with objectively verified VTE. To estimate adjusted hazard ratios for VTE, categorical and continuous spline models were fit by using Cox regression with shared-frailty or random-effect meta-analysis. A total of 1178 VTE events occurred over 599 453 person-years follow-up. Relative to eGFR 100 mL/min per 1.73 m<sup>2</sup>, hazard ratios for VTE were 1.29 (95% confidence interval, 1.04–1.59) for eGFR 75, 1.31 (1.00–1.71) for eGFR 60, 1.82 (1.27–2.60) for eGFR 45, and 1.95 (1.26–3.01) for eGFR 30 mL/min per 1.73 m<sup>2</sup>. In comparison with an albumin-to-creatinine ratio (ACR) of 5.0 mg/g, the hazard ratios for VTE were 1.34 (1.04–1.72) for ACR 30 mg/g, 1.60 (1.08–2.36) for ACR 300 mg/g, and 1.92 (1.19–3.09) for ACR 1000 mg/g. There was no interaction between clinical categories of eGFR and ACR ( $P=0.20$ ). The adjusted hazard ratio for CKD, defined as eGFR <60 mL/min per 1.73 m<sup>2</sup> or albuminuria ≥30 mg/g, (versus no CKD) was 1.54 (95% confidence interval, 1.15–2.06). Associations were consistent in subgroups according to age, sex, and comorbidities, and for unprovoked versus provoked VTE, as well.

**Conclusions**—Both eGFR and ACR are independently associated with increased risk of VTE in the general population, even across the normal eGFR and ACR ranges. (*Circulation*. 2012;126:1964–1971.)

**Key Words:** albuminuria ■ chronic kidney disease ■ deep vein thrombosis ■ epidemiology ■ GFR ■ pulmonary embolism ■ thromboembolism

The overall incidence rate of venous thromboembolism (VTE) in developed countries is ≈1.5 per 1000 person-years, varying from <0.05 in children to nearly 10.0 per 1000 person-years in the older adults.<sup>1–4</sup> The 28-day case-fatality rate after a first VTE is as high as 11%.<sup>4</sup> Because none of the known VTE risk factors are present in up to 50% of VTE

cases,<sup>3</sup> identifying novel risk factors for VTE is the focus of intensive research.

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Clinical Perspective on p 1971

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Nephrotic syndrome and overt proteinuria are well-known risk factors for VTE.<sup>5,6</sup> Mild to moderate chronic kidney disease (CKD) is associated with a procoagulant profile<sup>7–12</sup> and might therefore also be related to VTE risk. Two recent studies suggested that CKD may be associated with increased VTE risk, with some conflicting results.<sup>13–15</sup> Of the 2 key CKD-defining kidney measures (ie, glomerular filtration rate [GFR] and albuminuria), in the Atherosclerosis Risks in Communities (ARIC) study, a significant association was found only between reduced GFR and VTE incidence,<sup>14</sup> whereas, in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, an association was observed only for elevated albuminuria.<sup>13</sup> Possible explanations for these inconsistent findings might be the limited statistical power of the individual studies and differences in study population characteristics or the selection of covariates.

Given the high prevalence of CKD (10%–16%) in the general adult population,<sup>16–19</sup> in-depth analysis of the association of CKD with VTE incidence is warranted. Hence, we conducted an individual-level meta-analysis of 5 prospective general population–based cohorts with information on GFR, albuminuria, and incident VTE. This report explores the separate and combined associations of GFR and albuminuria with the risk of VTE.

## Methods

### Study Selection Criteria

To select eligible studies, we used criteria similar to those of the CKD Prognosis Consortium<sup>20,21</sup>; eligible studies had to be community-based cohort studies with both baseline estimated glomerular filtration rate (eGFR) and urine albumin measurements. A PubMed search was performed on March 2, 2010 with the use of the following combination of terms: (eGFR OR GFR OR “glomerular filtration rate” OR “kidney function” OR “renal function” OR “microalbuminuria” OR albuminuria OR “albumin to creatinine ratio” OR ACR OR “urinary albumin concentration” OR UAC) AND (“venous thrombosis” OR “venous thromboembolism” OR “pulmonary embolism” OR “deep vein thrombosis” OR DVT) AND (adult [MeSH]) AND (humans [MeSH]). Two investigators (B.K.M. and R.T.G.) performed the search independently. No language or publication period restrictions were applied. Subsequently, we searched general population studies, with albumin-to-creatinine ratio (ACR) ascertainment, that participated in the CKD Prognosis Consortium<sup>21</sup> in PubMed for availability of VTE outcomes. Finally, additional eligible cohorts were sought during scientific meetings and via personal contacts. The ethical review committee of the University Medical Center of Groningen approved the project to receive and analyze the data. Review committees of each participating cohort approved sharing of the deidentified individual-level data and the conducted analyses presented in this article.

### Baseline Study Variables

GFR was estimated with the use of the CKD Epidemiology Collaboration equation that takes into account serum creatinine, age, sex, and race.<sup>22</sup> In 3 studies, serum creatinine was not standardized to isotope dilution mass spectrometry, hence we reduced the creatinine levels by 5%, the calibration factor used to adjust nonstandardized Modification of Diet in Renal Disease Study samples to isotope dilution mass spectrometry.<sup>23</sup> In a sensitivity analysis, GFR was estimated by the use of the Modification of Diet in Renal Disease equation.<sup>24</sup> Albuminuria was quantified by the ratio of urinary albumin to urinary creatinine excretion in a spot or 24-hour urine sample.<sup>25,26</sup> CKD was defined as eGFR <60 mL/min per 1.73 m<sup>2</sup> or ACR ≥30 mg/g, according to prevailing guidelines.<sup>25</sup> History of cardiovascular disease was defined as history of self-reported myo-

cardial infarction or stroke at study baseline. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting glucose concentration of ≥7.0 mmol/L (≥126 mg/dL), a nonfasting glucose concentration of ≥11.1 mmol/L (≥200 mg/dL), or the use of glucose-lowering drugs or self-reported diabetes mellitus. Smoking was dichotomized to current smokers versus former or nonsmokers. Hypercholesterolemia was defined as a total cholesterol concentration of ≥5.0 mmol/L (193 mg/dL) in patients with a history of myocardial infarction or stroke and as ≥6.0 mmol/L (232 mg/dL) in patients without a history of myocardial infarction and stroke. Body mass index (BMI) was calculated as measured body weight in kilograms divided by height in meters squared.

### Venous Thromboembolism

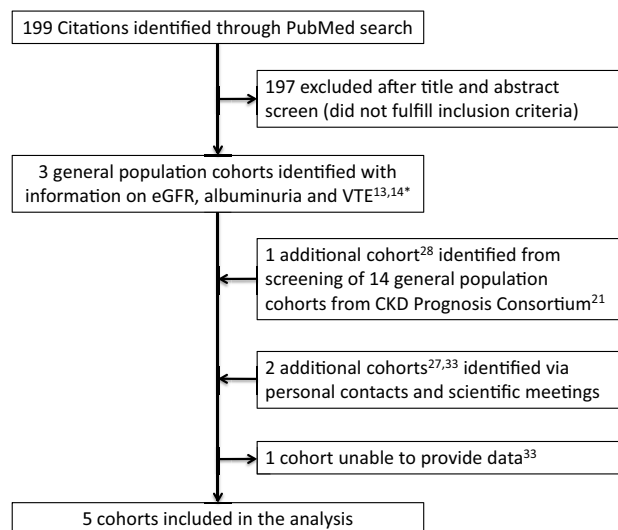
Only objectively verified symptomatic VTEs were considered in all cohorts. Deep vein thrombosis was confirmed by compression ultrasound or venography, and pulmonary embolism was confirmed by ventilation/perfusion lung scanning, angiography, spiral computed tomography, or at autopsy. Major trauma, surgery, significant immobilization, or active cancer in the preceding 3 months were the main determinants for classifying VTE as provoked.<sup>4,13,27,28</sup> Three of the 5 cohorts included additional risk factors in the definitions of provoked VTE, such as the use of oral contraceptives or hormone therapy, pregnancy, long-distance travel, active infectious disease, acute myocardial infarction, paresis/paralysis of the leg, and heart failure.<sup>13,27,28</sup> In the absence of the aforementioned risk factors, VTE was classified as unprovoked.

### Statistical Analysis

Individual participant data from the cohorts were pooled. Cox proportional hazards models with shared frailty (ie, random effects) were used to estimate adjusted hazard ratios (HRs) of VTE associated with eGFR, albuminuria, and their combination. Individual cohort was considered as the shared frailty variable to account for between-study differences. As sensitivity analysis, continuous eGFR and ACR associations with VTE were also modeled by using stratified (ie, fixed effects) Cox proportional hazards regression.

Based on previous literature on risk factors for VTE and correlates of eGFR and ACR, age, sex, BMI, history of cardiovascular disease, hypertension, diabetes mellitus, total cholesterol, and current smoking were included in models as potential confounders.<sup>13,14,29</sup> Because only 2 of the 5 studies also enrolled black participants, ethnicity-specific results were presented for those 2 studies rather than including race as a covariate in the main model. In addition, all eGFR models were adjusted for log-ACR, and all ACR models were adjusted for eGFR splines. To assess the shape of the relationship of eGFR and ACR with the risk of VTE, we modeled eGFR and ACR by using linear splines with knots at 45, 60, 75, 90, and 105 mL/min per 1.73 m<sup>2</sup> for eGFR, and 10, 30, 300, and 1000 mg/g (to convert to milligrams per millimole, multiply by 0.113) for ACR, respectively. eGFR of 100 mL/min per 1.73 m<sup>2</sup> and ACR of 5 mg/g were selected as reference points. HRs of eGFR association with VTE were estimated per 1 mL/min per 1.73 m<sup>2</sup> increment of eGFR from 15 to 120 mL/min per 1.73 m<sup>2</sup>. HRs for the association of ACR with VTE were estimated per 8% increments of ACR from 2.5 to 1000 mg/g. Adjustment for prevalent baseline traditional VTE risk factors (ie, major trauma, surgery, significant immobilization, or active cancer) was not performed because these were not uniformly available; however, given the temporary nature of these risk factors, baseline prevalence of these risk factors is unlikely to influence long-term VTE risk. To quantify short-term influence of these risk factors on the association of eGFR and albuminuria with VTE, we performed stratified analysis for provoked versus unprovoked VTE, where the definition of provoked VTE incorporated the presence of the traditional VTE risk factors.

Joint effects of eGFR and ACR on VTE were investigated by using cross-tabulation of eGFR and ACR categories. The interaction between eGFR and ACR was assessed by likelihood ratio tests between the models with eGFR and measured ACR with and without



**Figure 1.** Flow diagram for selection of studies. \*Reference 14 included analysis of 2 cohorts. eGFR indicates estimated glomerular filtration rate; VTE, venous thromboembolism; and CKD, chronic kidney disease.

their product terms. This methodology was also used to assess interactions of CKD with sex, race, age, hypertension, diabetes mellitus, smoking, hypercholesterolemia, history of cardiovascular disease, and BMI. Moreover, for dichotomous CKD VTE risk association, pooled estimates of the HRs and 95% confidence intervals (CIs) of individual studies were obtained from random-effects meta-analysis. Heterogeneity among studies was estimated by  $\chi^2$  test and the  $I^2$  statistics.<sup>30</sup> Potential sources of heterogeneity were explored by meta-regression analysis.

Because ACR was measured in only a subset of the second Nord-Trøndelag Health Study (HUNT2) cohort, we adjusted the eGFR-VTE associations for log-ACR values based on multiple imputation.<sup>31</sup> To achieve maximum accuracy for the imputed log-ACR, we created 20 complete data sets by the use of Stata ice command, which based the imputations on linear regression with bootstrap estimation method.<sup>31,32</sup> Subsequently the micombine command with Cox regression was used to obtain HRs and correct 95% CIs. Age, sex, hypertension, diabetes mellitus, a history of cardiovascular disease, VTE and log-transformed follow-up time were used to impute log-ACR values. To avoid potential bias due to multiple imputation, analyses of the ACR-VTE risk association were based on measured ACR values only. Statistical significance was considered as a 2-tailed  $P < 0.05$ . All statistical analyses were performed by the use of Stata software version 11.2 (StataCorp LP).

## Results

Figure 1 shows the flow diagram of the identified studies. Investigators of one of the eligible studies could not provide data.<sup>33</sup> Characteristics of the included studies are presented in Table 1. Overall, 95 154 participants (46.7% males, 96.6% whites) were included with 599 453 person-years of follow-up. During follow-up, 1178 VTEs occurred, 45% were classified as unprovoked, and 39% were pulmonary embolism alone or in combination with deep vein thrombosis. In all cohorts combined, 94 882 (99.7%) participants had measured eGFR data and 39 524 (41.5%) had ACR data (in HUNT2 only, 15% of participants had ACR measured;  $n = 9737$ ). All other variables presented in Table 1 had  $< 0.8\%$  missing values in the pooled data set, with the exception of current smoking (4.4% missing).

**Table 1. Study Characteristics per Cohort**

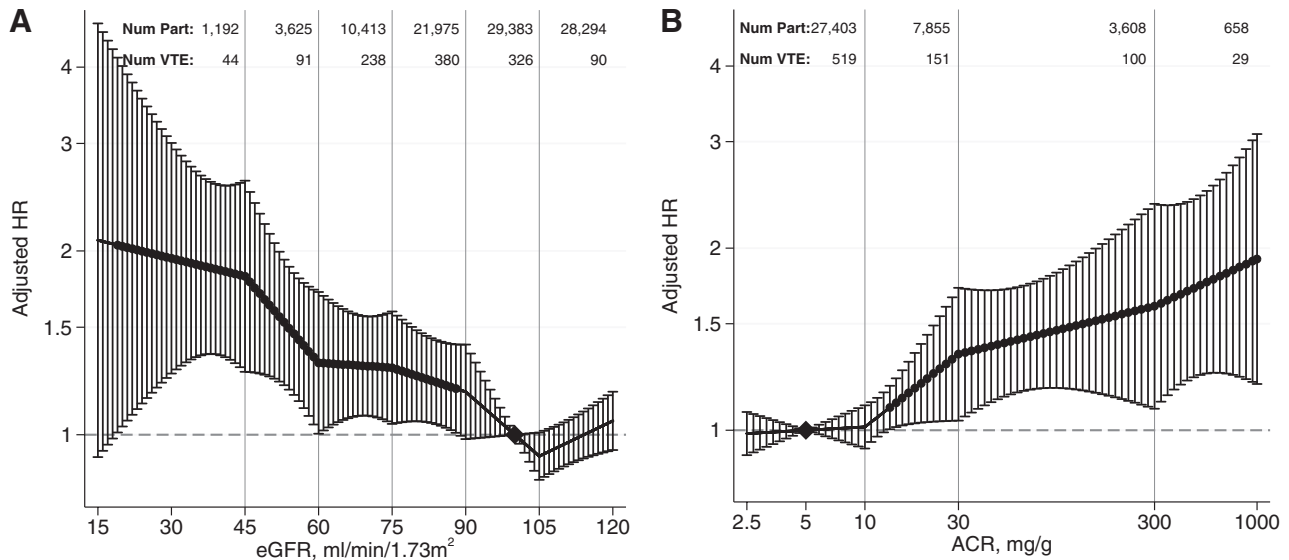
Country of Origin	ARIC* USA	CHS* USA	HUNT2 Norway	PREVEND Netherlands	Tromsø Norway
Baseline characteristics					
Participants, n	11 513	3450	64 793	8573	6825
Male, %	44.1	39.7	46.9	50.0	49.2
Mean age, y	62.8	78.1	50.2	49.0	60.2
Black, %	22.5	16.6	0.0	1.0	0.0
Hypertension, %	47.7	72.5	45.1	34.1	50.2
Diabetes, %	16.8	22.2	3.0	4.4	3.4
Hypercholesterolemia, %	21.2	27.3	46.6	37.9	70.8
Current smoking, %	14.8	7.6	29.8	34.2	31.8
History of MI or stroke, %	10.1	16.5	4.9	4.5	8.5
Mean body mass index, kg/m <sup>2</sup>	28.8	26.9	26.3†	26.1	26.0
Mean total cholesterol, mg/dL	200	203	228	218	259
Mean eGFR, mL/min per 1.73 m <sup>2</sup>	84.3	67.6	97.9	88.8	92.8
Median ACR, mg/g	3.7	10.2	7.7	7.0	5.4
Mean follow-up, y	8.0	4.5	5.2	9.3	10.8
Venous thromboembolism, n	260	61	509	122	226

eGFR was estimated by the CKD-EPI equation.<sup>22</sup> To convert total cholesterol to millimoles per liter, multiply by 0.0259. To convert ACR to milligrams per millimole, multiply by 0.113. MI indicates myocardial infarction; ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CKD-EPI, CKD Epidemiology Collaboration; and BMI, body mass index.

\*Because albuminuria was measured at visit 4 in ARIC and the year 7 in CHS, we treated these visits as the baseline for ARIC and CHS.

†In subjects with measured ACR in the HUNT2 study, mean BMI was 28 kg/m<sup>2</sup> as depicted in online-only Data Supplement Figure IV.





**Figure 2.** Pooled hazard ratios and 95% CIs for venous thromboembolism according to spline estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR). Hazard ratios and 95% confidence intervals (error bars) according to eGFR (A) and ACR (B) adjusted for each other, age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes mellitus, smoking, and total cholesterol. The reference (diamond) was eGFR 100 mL/min per 1.73 m<sup>2</sup> and ACR 5 mg/g (0.6 mg/dL), respectively. Black dots represent statistical significance. To convert ACR to milligrams per millimoles multiply by 0.113. Num Part and Num VTE indicate the number of participants and number of VTE, respectively, in the range between the knots represented by the vertical gray lines; CI, confidence interval; and VTE, venous thromboembolism.

Estimates of adjusted HRs for VTE according to eGFR and ACR levels are presented in Figure 2. Risk of VTE started to be significantly increased at eGFR 88 mL/min per 1.73 m<sup>2</sup>. Relative to eGFR 100 mL/min per 1.73 m<sup>2</sup>, HRs for VTE were 1.29 (95% CI, 1.04–1.59) for eGFR 75, 1.31 (1.00–1.71) for 60, 1.82 (1.27–2.60) for 45, and 1.95 (1.26–3.01) for 30 mL/min per 1.73 m<sup>2</sup>. Similar findings were observed in analyses with the use of the Modification of Diet in Renal Disease equation-based eGFR (online-only Data Supplement Figure I). The interpretation of results did not change in models comparing ACR as a covariate with and without the use of imputed ACR from the HUNT2 study, indicating the validity of the multiple imputation (online-only Data Supplement Figure II). The association of ACR splines and VTE risk was largely linear on the log-log scale, with significantly increased risk observed at ACR 14 mg/g and higher. In comparison with an ACR of 5.0 mg/g, the HRs for VTE were 1.34 (1.04–1.72) for 30 mg/g, 1.60 (1.08–2.36) for 300 mg/g, and 1.92 (1.19–3.09) for 1000 mg/g (Figure 2B). Results of fixed-effect Cox proportional hazards models were identical to the random-effect models (online-only Data Supplement Figure III).

Table 2 shows the adjusted HR of VTE in clinical categories of eGFR and ACR based on Kidney Disease Outcomes Quality Initiative (K/DOQI) staging.<sup>25</sup> The corresponding number of VTEs and total number of participants according to these categories are presented in online-only Data Supplement Table I. In general, the association of ACR with VTE risk was evident across most eGFR categories. The association between reduced eGFR and VTE risk was more obvious in those with normoalbuminuria (ie, ACR <30 mg/g). The risk increase was not clearly multiplicative with lower eGFR and higher ACR categories; tests for interaction

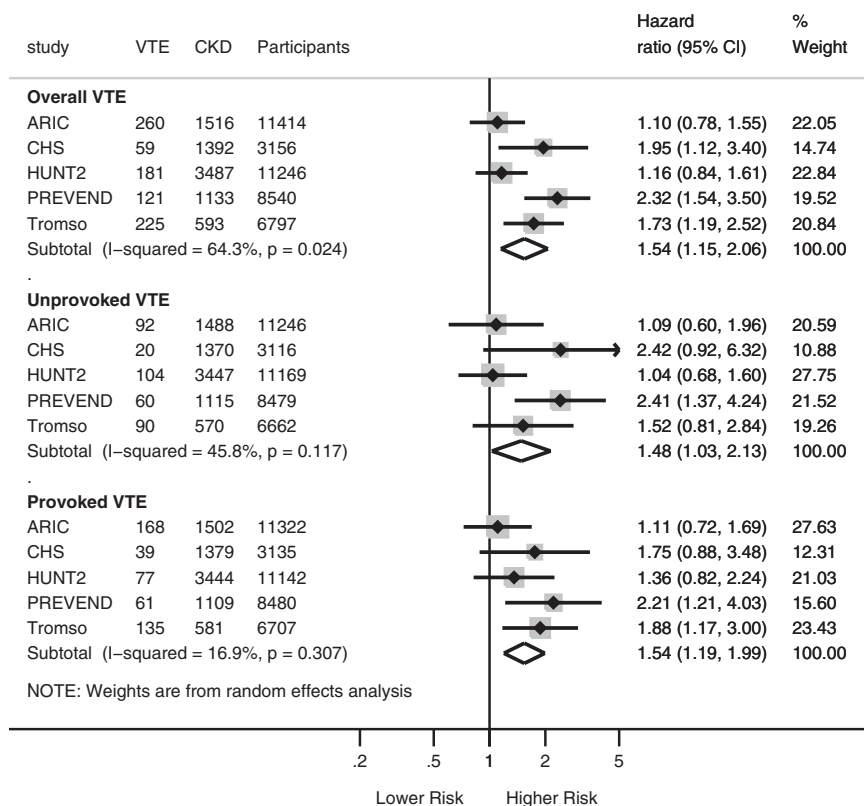
of the separate categories ( $P>0.14$ ) and overall ( $P=0.20$ ) were not significant. The interaction of continuous eGFR with spline terms and linear log-ACR was not significant ( $P=0.10$ ).

When we compared individuals with CKD versus no-CKD, the pooled HR for overall VTE associated with CKD was 1.54 (95% CI, 1.15–2.06) (Figure 3). In Figure 4, the impact of CKD on overall VTE incidence was consistent across the subgroups tested, with the exception of a trend for BMI categories showing weaker association of CKD with VTE in

**Table 2. Pooled Estimates of Adjusted Hazard Ratios (95% Confidence Intervals) for Venous Thromboembolism According to Clinical Categories of eGFR and ACR**

	ACR		
	<30 mg/g (<3.3 mg/dL)	30–300 mg/g (3.4–33.8 mg/dL)	>300 mg/g (≥33.9 mg/dL)
<b>eGFR</b>			
≥90 mL/min per 1.73 m <sup>2</sup>	Reference	1.66 (1.11–2.48)	1.51 (0.48–4.73)
60–89 mL/min per 1.73 m <sup>2</sup>	1.15 (0.96–1.38)	1.47 (1.07–2.03)	4.38 (2.64–7.26)
45–59 mL/min per 1.73 m <sup>2</sup>	1.23 (0.87–1.74)	1.37 (0.76–2.49)	1.51 (0.48–4.77)
30–44 mL/min per 1.73 m <sup>2</sup>	2.13 (1.26–3.62)	2.11 (0.95–4.95)	2.33 (0.74–7.34)

From the HUNT2 study, only subjects with measured ACR contributed to this analysis. eGFR was estimated by the CKD-EPI equation.<sup>22</sup> Given the low numbers of individuals with eGFR <30 (see online-only Data Supplement Table I), these individuals were excluded from this analysis. eGFR indicates estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio; CKD, chronic kidney disease; and CKD-EPI, CKD Epidemiology Collaboration.



**Figure 3.** Overall and study-specific hazard ratios for overall, unprovoked, and provoked venous thromboembolism in participants with CKD in comparison with those without CKD. CKD was defined by eGFR of  $<60$  mL/min per  $1.73$  m<sup>2</sup> and/or ACR  $\geq 30$  mg/g.<sup>25</sup> Hazard ratios are adjusted for age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes mellitus, smoking, and total cholesterol. The slight differences in numbers with Table 1 are due to missing observations for either eGFR or ACR, and because, for defining non-CKD, both eGFR and ACR were required. For the HUNT2 study only, measured ACR was considered in this analysis. eGFR indicates estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio; VTE, venous thromboembolism; and CKD, chronic kidney disease; and CI, confidence interval.

subjects with BMI  $\geq 25$  versus  $<25$  kg/m<sup>2</sup> ( $P$  for interaction=0.06). Similarly, the significant heterogeneity observed for overall VTE among studies appeared to be due to differences in BMI across studies ( $\beta = -0.23$ ,  $P = 0.054$ ) (online-only Data Supplement Figure IV).

The HRs of VTE with CKD in comparison with no CKD were similar for unprovoked and provoked VTE (Figure 3). Analyses for continuous eGFR and ACR are presented in the online-only Data Supplement Figure V. Similarly, the HRs of pulmonary embolism and deep vein thrombosis with CKD were similar (online-only Data Supplement Figure VI). Finally, of the covariates, only BMI and age showed significant strong association with VTE in all models of eGFR and ACR (data not shown).

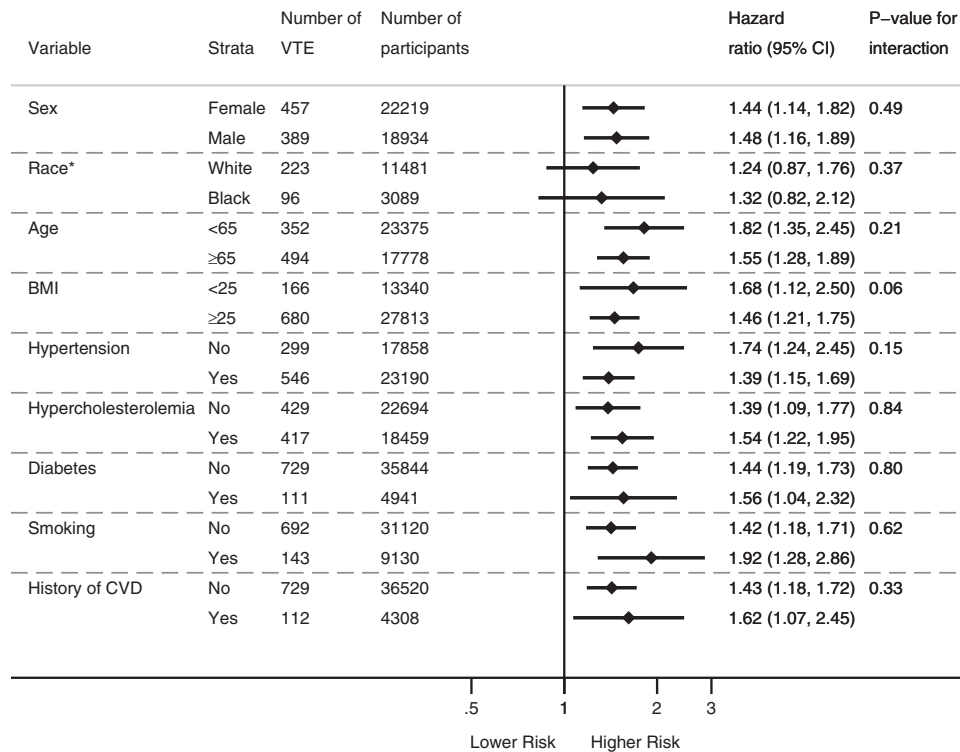
## Discussion

In this individual participant meta-analysis including 95 154 participants from prospective observational studies followed for an average of 6.3 years, both eGFR and elevated albuminuria were associated with increased risk of VTE independently of each other and traditional cardiovascular risk factors including BMI. For both eGFR and ACR, there was a dose-response relationship with increased risk of VTE starting in the non-CKD range of eGFR (ie,  $\geq 60$  mL/min per  $1.73$  m<sup>2</sup>) and the normal range of ACR (ie,  $<30$  mg/g). There was no significant interaction between eGFR and ACR. CKD, defined by eGFR  $<60$  mL/min per  $1.73$  m<sup>2</sup> or ACR  $\geq 30$  mg/g, was similarly associated with both provoked and unprovoked VTE and with both pulmonary embolism and deep-vein thrombosis.

In this comprehensive analysis of large prospective general population-based cohorts, a clear association of eGFR and albuminuria with risk of VTE clarifies the previous inconsistent published findings of the ARIC and PREVEND studies. In addition to ARIC and PREVEND cohorts, this analysis included previously unpublished data from 3 additional cohorts. The association of CKD with VTE was largely consistent in the presence versus the absence of various traditional cardiovascular risk factors, with the exception of a trend for relatively stronger association of CKD with VTE in subjects with BMI  $<25$  kg/m<sup>2</sup> in comparison with BMI  $\geq 25$  kg/m<sup>2</sup> ( $P = 0.06$ ). Difference in mean BMI among studies also explained most of the variability of the CKD-VTE risk association across studies. This finding is in line with several observational studies that reported an antagonistic interaction between BMI and CKD on mortality.<sup>34</sup>

The observation that risks do not fully multiply when both eGFR is low and ACR is high might be secondary to competing risk for mortality in low eGFR and high ACR categories, and to limited power in the low-eGFR and high-albuminuria categories, as well (online-only Data Supplement Table I). However, a significant interaction between eGFR and ACR categories in relation to mortality was not observed in a recent meta-analysis.<sup>21</sup>

CKD is associated with a broad range of diseases requiring hospitalization. This may have resulted in the association between CKD and provoked VTE. However, the association of eGFR and albuminuria with unprovoked VTE gives credence to a direct association of CKD with VTE. The high risk of VTE in individuals diagnosed with nephrotic-range proteinuria is assumed to be secondary to the loss of antico-



**Figure 4.** Association of CKD with VTE in subgroups according to traditional cardiovascular risk factors. CKD was defined by eGFR of <60 mL/min per 1.73 m<sup>2</sup> or ACR ≥30 mg/g.<sup>25</sup> Hazard ratios are adjusted for other than the stratified risk factor itself, which included age, sex, body mass index, history of cardiovascular disease, hypertension, diabetes mellitus, smoking, and total cholesterol. \*Race comparison was limited to ARIC and CHS studies, because the other studies enrolled only whites. CVD indicates cardiovascular disease; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio; VTE, venous thromboembolism; and CKD, chronic kidney disease; HR, hazard ratio; CI, confidence interval; and BMI, body mass index.

agulant proteins.<sup>6</sup> The increased risk of VTE with mild to moderate CKD may be secondary to endothelial injury and the related changes in procoagulant proteins such as increased levels of fibrinogen, factor VII, factor VIII, von Willebrand factor, and plasminogen activator inhibitor-1 or increased levels of D-dimers.<sup>7–12</sup> An increased procoagulant state in CKD patients was also confirmed by functional coagulation assays such as prothrombin fragment 1+2, thrombin–anti-thrombin complex, plasmin–antiplasmin complex, and in vitro thrombin generation assessed by a calibrated automated thrombogram, as well.<sup>7,8,10,35</sup> The well-known link of CKD with arterial cardiovascular disease and mortality<sup>36</sup> is also assumed to be at least partially due to a hypercoagulable state.<sup>7,8,10</sup>

The high prevalence of CKD in the general population (10%–16%) suggests that, on the population level,<sup>16–19</sup> CKD may explain a much larger proportion of VTE risk than most of the established rare hereditary VTE risk factors, such as antithrombin, protein C, and protein S deficiencies.<sup>37</sup> Assuming a CKD prevalence of 10% in the general population, the observed HR of 1.54 in our study corresponds to a population-attributable risk of 5.1%, if the relationship is causal. In contrast to most established VTE risk factors, CKD, in particular, albuminuria, is modifiable with medications (eg, renin-angiotensin system inhibitors).<sup>38,39</sup> In fact, losartan use in patients with overt proteinuria >2.0 g/d ameliorates the hypercoagulable state in proteinuric patients.<sup>35</sup> Taken together with our findings, studies evaluating

the effect of albuminuria-lowering drugs on the risk of VTE in patients with mild to moderate CKD are warranted. Furthermore, because CKD is common, based on the current findings, it would be useful to assess whether CKD might be associated with the risk of recurrent VTE.

We acknowledge that this study has limitations. First, the measurement of creatinine, albuminuria, and potential confounders was not standardized among all studies. For instance, some studies measured albumin and creatinine in fresh urine samples, whereas other studies used frozen samples, and there was no centralized laboratory for all studies together. Care was taken, however, to use the same definitions for exposure variables and covariates across studies. Second, whereas we accounted for cardiovascular risk factors as potential confounders that are strongly associated with CKD and possibly associated with VTE, residual confounding may still remain. Although we were not able to account for hereditary thrombophilic defects, these are not known to be associated with mild to moderate CKD. In fact, 1 recent study reported a renoprotective effect of factor V Leiden.<sup>40</sup> Third, event ascertainment across studies was comparable, but the definitions of unprovoked and provoked VTE were slightly different. However, we observed largely consistent findings for the association of CKD with overall, unprovoked, and provoked VTE. Fourth, we are unable to account for anticoagulant medication use. However, given that CKD is associated with cardiovascular disease, ignoring anticoagulant medication use would have resulted in underestimated

CKD-VTE risk association. Last, meta-regression analysis that explored the variation of HRs across studies was underpowered given the small number of studies in current analysis. Nevertheless, the association of BMI with the variation of HRs of the association of CKD with VTE risk reached borderline significance, suggesting that the heterogeneity across studies might be secondary to differences in mean BMI.

In conclusion, both eGFR and ACR are independently associated with increased risk of VTE in the general population, even in the non-CKD range of eGFR and the normal range of ACR.

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### Disclosures

None.

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## CLINICAL PERSPECTIVE

Chronic kidney disease (CKD) is a major health problem that affects 10% to 16% of the general adult population. Whereas associations of CKD with arterial thromboembolism and mortality are well known, the association of CKD with venous thromboembolism (VTE) is uncertain. In the present study, we assessed the association of CKD with venous thrombosis in 5 general population cohorts. The key CKD measures (ie, decreased estimated glomerular filtration rate and elevated albumin-to-creatinine ratio) were both associated with an increased risk of VTE, even for values in the normal ranges. Subjects with CKD (ie, estimated glomerular filtration rate <60 mL/min per 1.73 m<sup>2</sup> or albumin-to-creatinine ratio ≥30 mg/g) had a 54% higher risk of VTE in comparison with subjects without CKD. The associations were similar for unprovoked and provoked VTE, and for pulmonary embolism and deep-vein thrombosis, as well. CKD measures showed largely similar associations with VTE across subgroups of traditional cardiovascular risk factors, such as hypertension, diabetes, age, and sex. Given the effect size of the association, individual-level implications may be limited. Nevertheless, because of the high prevalence of CKD, population-level VTE burden owing to CKD is estimated to be high, especially in populations with high CKD prevalence such as those with diabetes mellitus and hypertension. Future studies are warranted to assess whether CKD is also associated with recurrent VTE. If confirmed, these findings may have implications for the duration of anticoagulant treatment for first VTE.